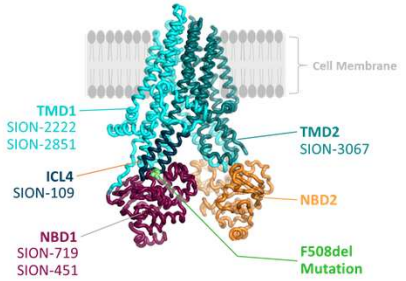
# Safety, Tolerability, and Pharmacokinetics of Novel NBD1 Stabilizers SION-719 and SION-451 from Two Phase 1 First-in-Human Studies

Jason Maley, Heather Wolff, Jessica Hauben, Steve Altmann, Gregory Hurlbut, Kenneth Huttner, Monette Cotreau, Shane Raines, and Charlotte McKee
Sionna Therapeutics, Waltham, MA

DISCLOSURE: All authors are Sionna Therapeutics employees or paid consultants. Sionna employees hold stock or stock options in Sionna Therapeutics.

## Background

- Despite treatment advances, ***over two-thirds of patients on ETI and VTD have abnormal CFTR function***[1,2,3] as measured by sweat chloride >30mmol/L
- ***F508del defect resides within the nucleotide-binding domain 1 (NBD1)*** of CFTR and severely destabilizes NBD1, preventing normal CFTR folding, domain assembly, trafficking, protein half-life, and function[4]
- Sionna NBD1 stabilizers are the ***first and only small molecules to directly bind to and stabilize NBD1*** at physiological concentrations[4]
- NBD1 stabilizers, combined with other modulators that improve domain-domain assembly, have the ***potential to fully correct F508del-CFTR function***[4]




## Methods and Cohort Design

- Two Phase 1 studies assessed ***safety, tolerability, and PK*** of single and multiple ascending doses of ***SION-719 and SION-451*** in healthy volunteers
- ***Randomized, double-blind, placebo-controlled*** studies (6 received active drug and 2 received placebo, per dose-level)
- Single ascending dose (SAD) and 10-day multiple ascending dose (MAD) parts dosed as oral suspension (fasted unless noted)
- Evaluated the ***effect of food on PK, and the bioequivalence*** (FE/BE) of a tablet formulation compared to oral suspension

**SION-719**

- 100 participants dosed
- SAD: 20mg (fasted & fed), 40mg, 80mg, 160mg
- MAD (BID): 20mg, 40mg, 80mg, 120mg, 160mg
- FE/BE: doses in add-on to standard-of-care (SOC) modulators and dual combo ranges

**SION-451**

- 110 participants dosed
- SAD: 25mg (fed), 75mg (fasted & fed), 150mg, 300mg, 450mg
- MAD (BID): 25mg (fed), 75mg, 150mg, 225mg, 300mg
- FE/BE: doses in add-on to SOC modulators and dual combo ranges

TMD – Transmembrane Domain 1 and 2 of CFTR; ICL4 – Intracellular Loop 4 of CFTR

*1. Konstan et al., Abstract #43. NACFC 2022; 2. Zemanick et al., JCF 2024 Jul 1;23(4):676–84.; 3. Keating et al. Lancet Resp Med. 2025 Mar 1;13(3):256–71. 4. ECFS 2025, Hurlbut et al. Abstract WS19.01.*

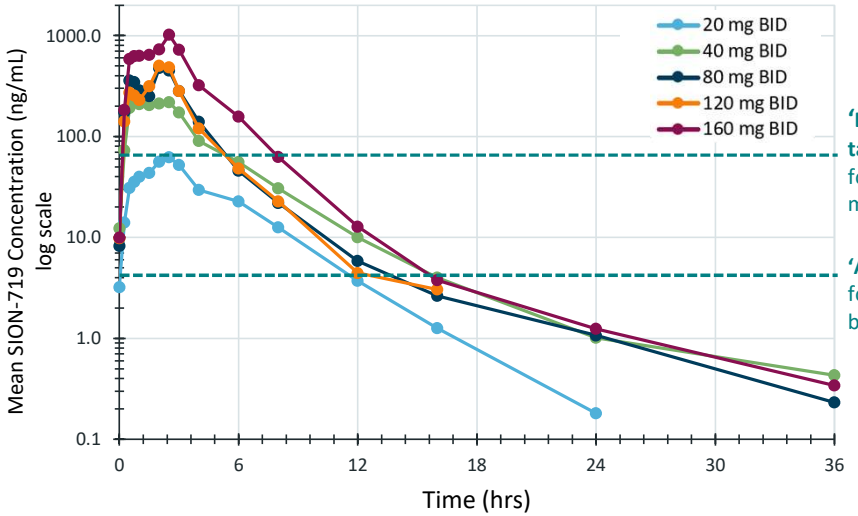
# **SION-719 Results**: *Generally safe and well tolerated* in healthy volunteers and *exceeded CFHBE-based concentration targets*

## 10-Day MAD Treatment-Emergent Adverse Events

| Study Participants (n)* | Placebo BID (n=10) | 20 mg BID (n=6) | 40 mg BID (n=6) | 80 mg BID (n=6) | 120 mg BID (n=6) | 160 mg BID (n=6) | MAD Total (n=40) |
|---|---|---|---|---|---|---|---|
| **Any TEAE, n (%)** | **4 (40)** | **2 (33)** | **4 (67)** | **6 (100)** | **5 (83)** | **3 (50)** | **24 (60)** |
| Mild (Grade 1) | 3 (30) | 2 (33) | 3 (50) | 5 (83) | 2 (33) | 3 (50) | 18 (45) |
| Moderate (Grade 2) | 1 (10) | - | 2 (33) | 1 (17) | 3 (50) | 1 (17) | 8 (20) |
| Severe (Grade 3) | - | - | - | - | - | - | - |
| Life-threatening (Grade 4) | - | - | - | - | - | - | - |
| Leading to treatment discontinuation | - | - | - | - | - | - | - |
| **Serious TEAEs, n (%)** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |
| **Most frequent TEAEs (≥2 subjects), n (%)** | | | | | | | |
| Headache | - | - | 4 (67) | 1 (17) | 2 (33) | 2 (33) | 9 (23) |
| Diarrhea | 1 (10) | 1 (17) | - | - | - | 2 (33) | 4 (10) |
| Nausea | 1 (10) | - | 1 (17) | - | - | 1 (17) | 3 (8) |
| Catheter site phlebitis | - | - | - | - | 2 (33) | - | 2 (5) |
| Pruritus | 1 (10) | - | - | - | - | 1 (17) | 2 (5) |

- SAD and MAD with overall consistent safety profile
- No SAEs; all TEAEs mild to moderate (Grade 1 or 2)
- No TEAEs led to drug discontinuation and no dose-limiting TEAEs observed
- No TEAEs related to increased liver enzymes
- No clinically meaningful trends in other safety parameters, vital signs or ECG

## **Steady State MAD PK:** Day 10 Through 36 Hours Post-administration




*Each solid line shows mean concentration data from a dosing cohort on Day 10*

PK observations in the SAD portion of the trial were generally consistent with the MAD findings shown; SOC –standard of care

- Add-on to SOC target coverage based on CFHBE assay at all doses studied
- Dual combination coverage based on CFHBE assay at ≥40mg BID
- High potency and synergy with SOC support lower dose SION-719 for Phase 2a POC
- FE/BE data
  - Support use of the tablet in future studies
  - Indicate SION-719 can be dosed in fed or fasted state

# **SION-451 Results**: *Generally safe and well tolerated* in healthy volunteers and *exceeded CFHBE-based concentration targets*

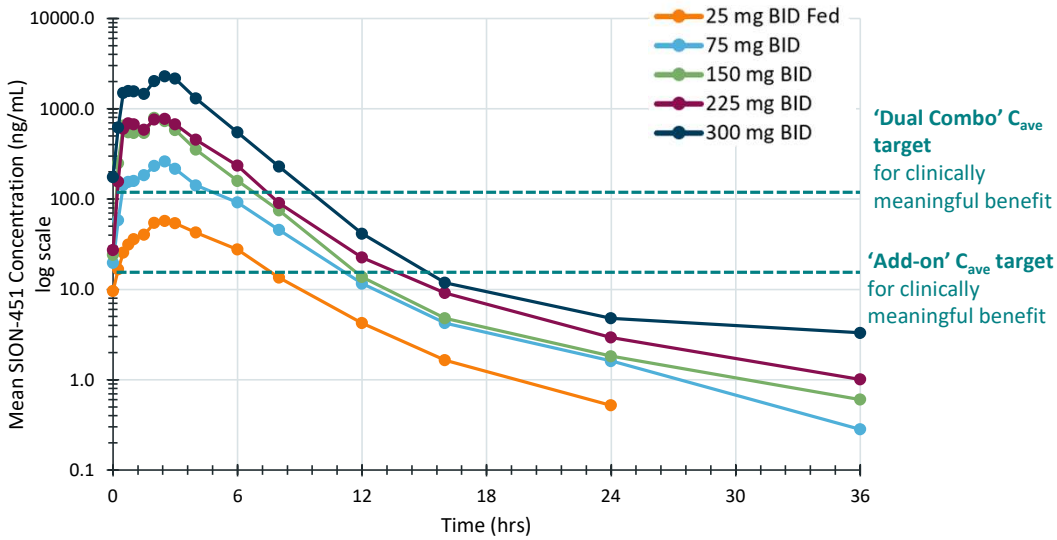
## 10-Day MAD Treatment-Emergent Adverse Events

| Study Participants (n)* | Placebo BID (n=9) | 25 mg BID (n=6) | 75 mg BID (n=5) | 150 mg BID (n=6) | 225 mg BID (n=6) | 300 mg BID (n=6) | MAD Total (n=38) |
|---|---|---|---|---|---|---|---|
| **Any TEAE, n (%)** | **5 (56)** | **2 (33)** | **3 (60)** | **3 (50)** | **4 (67)** | **2 (33)** | **19 (50)** |
| Mild (Grade 1) | 4 (44) | 2 (33) | 2 (40) | 1 (17) | 4 (67) | - | 13 (34) |
| Moderate (Grade 2) | 1 (11) | - | 1 (20) | 1 (17) | - | 2 (33) | 5 (13) |
| Severe (Grade 3) | - | - | - | 1 (17) | - | - | 1 (3) |
| Life-threatening (Grade 4) | - | - | - | - | - | - | - |
| Leading to treatment discontinuation | - | - | - | - | - | - | - |
| **Serious TEAEs, n (%)** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |
| **Most frequent TEAEs (≥2 subjects), n (%)** | | | | | | | |
| Headache | 3 (33) | 1 (17) | - | - | 2 (33) | 1 (17) | 7 (18) |
| Influenza | - | - | - | 2 (33) | - | - | 2 (5) |
| Upper Respiratory Tract Infection | 1 (11) | - | - | 1 (17) | - | - | 2 (5) |

- SAD and MAD overall consistent safety profile
- No SAEs; most TEAEs mild to moderate (Grade 1 or 2)
- No TEAEs led to drug discontinuation and no dose-limiting TEAEs observed
- One Grade 1 TEAE related to elevated liver enzymes in treated subject who tested positive for influenza[1]; no TEAEs related to liver enzymes in other cohorts
  - Same subject had transient Grade 3 neutropenia at same time as influenza
- No clinically meaningful trends in other safety parameters, vital signs or ECG

1. Subject was in isolated dose cohort of SION-451 (150mg BID) that was impacted by an outbreak of respiratory infection

## **Steady State MAD PK:** Day 10 Through 36 Hours Post-administration




*Each solid line shows mean concentration data from a dosing cohort on Day 10*

- Dual combination target coverage based on CFHBE assay at ≥75 mg BID
- Add-on target coverage based on CFHBE assay at all doses studied
- High exposures support evaluating SION-451 upper dose range in Ph 1 Healthy volunteer dual combination
- FE/BE data
  - Support use of the tablet in future studies
  - Indicate SION-451 can be dosed in fed or fasted state

# Conclusions for SION-719 and SION-451

- Novel NBD1 stabilizers SION-719 and SION-451 were ***generally safe and well tolerated*** in healthy volunteers in these Phase 1 studies.
- Both compounds ***exceeded concentrations that, based on the CFHBE assay, have the potential to deliver clinically meaningful benefit*** when:
  - Added to existing SOC modulators
  - Used in a novel dual combination with one of Sionna's complementary modulators
- SION-719 and SION-451 tablets can be dosed ***fed or fasted*** based on FE/BE cohorts
- ***Novel NBD1s currently in two studies*** with anticipated near-term read-outs:
  - SION-719: PreciSION CF Phase 2a proof-of-concept, summer 2026
  - SION-451: Phase 1 dual combination studies with SION-2222 and SION-109, mid-2026